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Terramycin in Urinary Tract Infections

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SUMMARY

Terramycin® is an effective agent in the control of urinary tract infections with organisms of the enteric group.

The drug is tolerated by mouth and no serious side-reactions occur. In cases in which there is no organic or obstructive disease, the response to Terramycin as a urinary antiseptic is prompt and effective. In several cases in which there was severe organic and obstructive disease and the organism was highly resistant, the course of the disease was not altered by giving Terramycin.

TERRAMYCIN®* is a new antibiotic yielded by the recently discovered actinomycete, streptomyces rimosus. It is a crystalline amphoteric substance which can be chemically reacted with certain acids or bases to form crystalline salts. In the dry crystalline state Terramycin and its salts possess good stability at 25° C. A unit of Terramycin is equivalent to one microgram of the pure amphoteric compound. The activities of the salts of Terramycin are stated in terms of the equivalent weight of pure Terramycin. The hydrochloride, the sulfate and the true sodium salt of Terramycin have been shown to maintain their potency for several weeks at 50° C. Aqueous solutions of Terramycin showed no loss of potency in 20 days with a pH of 5.0 or below.

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*Terramycin is made by Charles Pfizer & Co., Inc.

ABSORPTION AND EXCRETION

The drug is rapidly absorbed by either the oral or parenteral route. After intramuscular injection it can be recovered in the bloodstream for 24 hours. Within two hours it appears in the urine in amounts proportionate to the serum concentration.

The absorption of Terramycin from the gastrointestinal tract results in a good serum concentration within a few hours, and as much as 40 per cent of a single oral dose has been recovered in the urine. It is probable that a considerable amount of Terramycin is excreted in the feces. It changes considerably the bacterial flora of the gastrointestinal tract. In the patients so far treated no deleterious effects were noted from the suppression of some organisms or over-growth of others in the intestines.

Terramycin, like other antibiotics, traverses the placental barrier and may be found in the cord blood. This is true after the administration of as little as 2 gm. during labor. It does not appear to have any harmful effects on the newborn.

MATERIALS AND METHODS

Terramycin was used in 32 instances for treatment of urinary tract infection in patients on the obstetrical and gynecological service. Cultures of urine and urinalyses were done daily, and sensitivity tests to the amphoteric and in some cases to the hydrochloride forms of Terramycin were run by the tube dilution method. The temperature chart, the amount of pyuria, symptoms and the degree of control of the bacilluria were observed to evaluate the effectiveness of the agent. Results were considered to be good, equivocal, or poor on the following basis: A good result was recorded when in 72 hours or less the temperature fell to normal, the pyuria cleared, a negative culture was obtained and the pa-

tient was symptom-free. Equivocal results were recorded when those responses did not take place until later, or when bacilluria with mild symptoms persisted, although the other criteria were met. If Terramycin did not alter the course of the disease, the result was recorded as poor.

The group of patients treated included some with mild infections such as postoperative cysto-ureteritis and pyelonephritis of pregnancy. Several had severe organic and obstructive disease of the urinary tract. These patients had operations such as radical removal of carcinoma of the cervix with bilateral nephrostomy, wet colostomy with uretero-intestinal anastomosis or skin transplants.

DOSAGE AND TOLERANCE

A suggested dosage schedule is shown in Table 1. If the patient has no organic or obstructive disease, a dose of 250 mg. every six hours for the first five days and 250 mg. twice a day for the following five days is recommended. If organic disease is present, the amount of Terramycin given should be doubled. It is usually important to continue therapy for ten days or longer to prevent relapse or persistent bacilluria. The drug was tolerated well except for transient nausea in a few instances. One severely ill patient who had had pelvic eviscerectomy for advanced cervical carcinoma had vomiting after starting Terramycin, but in that case the abdomen was distended and the patient was not tolerating anything by mouth very well. The drug could not, therefore, be directly indicted.

TABLE 1.—*Suggested Dosage Schedule for Terramycin (10 Days)*

	Days 1-5	Days 6-10
No organic or obstructive disease and B. coli or A. aerogenes isolated	250 mg. every six hours	250 mg. twice daily
With organic or obstructive disease or if Ps. aeruginosa or P. vulgaris is isolated	500 mg. every six hours	250 mg. every six hours

COMPARATIVE SENSITIVITIES (IN VITRO)

It must be emphasized that the clinical effectiveness of a drug does not necessarily parallel the in vitro sensitivity determined for the organism isolated in the case. Sensitivity tests roughly indicate susceptible organisms, but exceptions are repeatedly noted. Forty organisms isolated from the urinary tract were tested against the amphoteric form of Terramycin. Wide variations in resistance were noted (Table 2). Nineteen organisms were tested against Terramycin, aureomycin and chloramphenicol for comparison. Tables 3 and 4 show the results of this study.

RESULTS OF THERAPY

The results with Terramycin were uniformly good in cases in which no organic or obstructive disease existed (Table 5). The patients with pyelitis of pregnancy or simple postoperative cysto-ureteritis responded very promptly to Terramycin. There was a prompt drop in temperature, disappearance of pyuria and bacilluria, and symptomatic relief. In three instances P. vulgaris replaced the original offender in the follow-up cultures, but the patient was asymptomatic. The effect of Terramycin is remarkably like that of aureomycin in infection of this type. This observation is based on a comparison of results obtained with Terramycin with those obtained in a large group of similar cases in which aureomycin was used on the same dosage schedule.

Five patients with organic or obstructive disease were treated. One had had pelvic eviscerectomy for advanced cervical carcinoma. She had a colostomy and bilateral ureterocutaneous transplants which

TABLE 2.—*Terramycin (Amphoteric Form)* Sensitivity tests (mcg./ml.)*

	No. organisms	0.2	0.4	0.8	1.6	3.13	6.25	12.5	25	50	>50
Ps. aeruginosa	18	....	....	....	....	....	1	1	4	3	9
A. aerogenes	10	1	....	2	3	1	1	....	1	1	....
B. coli	10	....	....	1	1	2	1	....	1	2	2
P. vulgaris	2	....	....	....	....	....	....	....	....	....	2

*Organisms isolated from urinary tract.

TABLE 3.—*Comparative Sensivity (in Vitro)** Strains of Ps. aeruginosa (mcg./ml.)

11 Organisms	Aureomycin	Chloramphenicol	Terramycin
1	0.4	6.25	6.25
2	12.5	50	50
3	50	50	>50
4	1.6	6.25	25
5	>50	>50	25
6	50	50	>50
7	50	50	>50
8	>50	50	>50
9	50	>50	25
10	>50	50	>50
11	>50	50	>50

*Organisms isolated from urinary tract.

TABLE 4.—*Comparative Sensitivity (in Vitro)** (mcg/ml.)

Organisms	Aureomycin	Chloramphenicol	Terramycin
A. aerogenes	50	50	25
A. aerogenes	0.8	6.25	0.8
A. aerogenes	3.13	3.13	6.25
A. aerogenes	0.4	6.25	0.2
B. coli	50	50	50
B. coli	>50	>50	25
B. coli	25	25	3.13
P. vulgaris	25	25	>50

*All organisms isolated from urinary tract.

TABLE 5.—*Terramycin Therapy in 32 Urinary Tract Infections*

Organism	No. Cases	Results		
		Good	Equivocal	Poor
No organic or obstructive disease:				
B. coli	15	14	1	0
A. aerogenes	4	4	0	0
Aerobic diphtheroids	3	2	1	0
S. albus	2	2	0	0
Aerobic non-hemolytic streptococcus	2	2	0	0
Ps. aeruginosa	1	0	1	0
With organic or obstructive disease:				
Ps. aeruginosa	3	1	0	2
P. vulgaris	1	0	1	0
A. aerogenes	1	1	0	0
Totals	32	26	4	2

were functioning well. Ps. aeruginosa were repeatedly cultured from both sides. On Terramycin therapy there was a period of over two days when several cultures were negative for the organism. Subsequently, however, cultures were positive for Ps. aeruginosa despite continuation of the therapy.

Another patient had a Stage IV carcinoma of the cervix. Bilateral nephrostomy had been done because of ureteral obstruction and uremia. Cultures consistently grew Ps. aeruginosa. Again, for a transient period after the start of therapy a few cultures were negative for the organism but the patient continued febrile and there was no lessening of pyuria. The course of the infection and disease was not altered by Terramycin.

Another of the five patients had had radical excision of the cervical stump for carcinoma. Complete bilateral pelvic lymphadenectomy had been carried out, with the usual postoperative neurogenic bladder. In addition, there was a double ureter on the right side, both parts of which emptied into the bladder with separate orifices. There was no hydronephrosis at the time the patient was treated: An indwelling catheter had been placed because of urinary retention. Cultures showed Ps. aeruginosa. Bacilluria, pyuria and pain in the right costovertebral angle abated promptly when Terramycin was given. There was no relapse and the results in this case were considered good.

The fourth patient, 34 weeks pregnant, had tuberculosis of the left kidney and a ureterocutaneous transplant had been done. The right kidney had been removed. Acid-fast bacilli were observed on one smear but not on cultures. P. vulgaris was found in the routine cultures and several cultures also grew Ps. aeruginosa. Terramycin was given as shown in the dosage schedule, and 15 cc. of para-aminosalicylic acid was given four times a day. Pyuria cleared and pain and tenderness in the left costovertebral angle disappeared. The P. vulgaris was replaced by A. aerogenes and the latter grew on every subsequent culture despite continued therapy. This was a strange reversal of the usual picture in that an organism which usually is very sensitive replaced a resistant one. The result was considered equivocal because, although the patient had no pyuria or symptoms, bacilluria persisted. Para-aminosalicylic acid was continued for several additional weeks. After the start of therapy, acid-fast bacilli were not demonstrated on cultures and could not be recovered from inoculated guinea pigs. The patient had uneventful delivery at term.

The fifth patient in the group had recurrent carcinoma of the endometrium with carcinomatosis. A space-occupying lesion of the left kidney was observed in an intravenous pyelogram. No hydronephrosis was observed, and A. aerogenes grew on cultures. Terramycin was given, the urine promptly became sterile, pyuria cleared and the patient became symptom-free.

This new drug mathematically extends the number of combinations of antibiotics and other urinary tract antiseptics that can be used. If symbiotic action can be proved, then the greatest field of usefulness may lie in determining the combinations that are effective in any given resistant organism, long-standing organic disease, or after radical operation with ureteral transplants and obstructive disease.